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Population pharmacokinetics of intravenous pantoprazole in paediatric intensive care patients

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The use of intravenous pantoprazole, a proton pump inhibitor, has been increasing in the paediatric intensive care unit.
- Despite this increased use, data on the disposition of intravenous pantoprazole in paediatric intensive care patients are very scarce.

WHAT THIS STUDY ADDS

- Our population approach has determined the pharmacokinetic parameters of intravenous pantoprazole in paediatric intensive care patients and the relative importance of factors influencing its disposition.
- Pantoprazole clearance was significantly influenced by developmental changes and by the presence of systemic inflammatory syndrome, hepatic dysfunction and CYP2C19 inhibitors.

AIMS

To characterize the pharmacokinetics of intravenous pantoprazole in a paediatric intensive care population and to determine the influence of demographic factors, systemic inflammatory response syndrome (SIRS), hepatic dysfunction and concomitantly used CYP2C19 inducers and inhibitors on the drug's pharmacokinetics.

METHODS

A total of 156 pantoprazole concentration measurements from 20 patients (10 days to 16.4 years of age) at risk for or with upper gastrointestinal bleeding, who received pantoprazole doses ranging from 19.9 to 140.6 mg/1.73 m^2/day, were analysed using a population pharmacokinetic approach (NONMEM program).

RESULTS

The best structural model for pantoprazole was a two-compartment model with zero order infusion and first-order elimination. Body weight, SIRS, age, hepatic dysfunction and presence of CYP2C19 inhibitors were significant covariates affecting clearance (CL), accounting for 75% of interindividual variability. Only body weight significantly influenced central volume of distribution (V_c). In the final population model, the estimated CL and V_c were 5.28 l h^{-1} and 2.22 l, respectively, for a typical 5-year-old child weighing 20 kg. Pantoprazole CL increased with weight and age, whereas the presence of SIRS, CYP2C19 inhibitors and hepatic dysfunction, when present separately, significantly decreased pantoprazole CL by 62.3, 65.8 and 50.5%, respectively. For patients aged between 6 months and 5 years without SIRS, CYP2C19 inhibitor or hepatic dysfunction, the predicted pantoprazole CL is faster than that reported in adults.

CONCLUSION

These results provide important information for physicians regarding selection of a starting dose and dosing regimens of pantoprazole for paediatric intensive care patients based on factors frequently encountered in this population.

Introduction

Paediatric intensive care patients require gastric acid suppression to prevent stress-related ulcer bleeding and to manage upper gastrointestinal bleeding. Despite limited data regarding the efficacy of proton pump inhibitors (PPIs) in the prevention of stress-related ulceration, the use of PPIs for this indication has dramatically increased in recent years [1, 2]. In addition, the superiority of intravenous (i.v.) PPIs over histamine$_2$ receptor antagonists for peptic ulcer bleeding [3] has led to the use of i.v. PPI therapy for the treatment of upper gastrointestinal bleeding in adult and paediatric intensive care patients [4, 5].

PPIs selectively and irreversibly inhibit gastric H^+/K^+-adenosine triphosphatase (ATPase), the proton pump that performs the final step of acid production by parietal cells. PPI inhibition of ATPase suppresses both basal and stimulated secretion of gastric acid independently of the nature of parietal cell stimulation [6]. The potent acid inhibitory action of PPIs translates to a significantly superior efficacy of these agents for acid-related disorders in adults compared with histamine$_2$ receptor antagonists [7]. During critical illness, PPIs offer advantages over histamine$_2$ receptor antagonists. For example, with PPI use there is no development of tolerance [8–10], no need for dosing adjustment for renal insufficiency [11–14] or during haemodialysis [15], and PPIs are well tolerated [7, 16].

Pantoprazole is an attractive choice for intensive care patients, as it appears to have a more limited potential for drug interactions compared with other PPIs [17]. In addition, the availability of an i.v. formulation eliminates problems associated with extemporaneous formulations of enteric-coated granules of PPIs that can potentially clog enteral feeding tubes, have variable bioavailability [18, 19] and require adequate absorptive capacity, which is often diminished in critically ill patients [20]. Furthermore, i.v. administration of a PPI is more efficient in achieving gastric acid suppression than oral administration [21].

To date, there are limited data regarding the pharmacokinetics of pantoprazole in children [22, 23], with essentially no data for infants <2 years old. Evaluation of i.v. pantoprazole administration in this population is supported by the pharmacokinetic–pharmacodynamic relationship for PPIs seen in adults [16, 24–26] and children [27–32]. For each PPI, the degree of acid suppression is correlated with systemic drug exposure reflected by the area under the plasma concentration–time curve (AUC).

The objectives of this study were to characterize the pharmacokinetics of i.v. pantoprazole in paediatric intensive care patients and to determine the influence of demographic factors, systemic inflammatory response syndrome (SIRS), hepatic dysfunction and concomitantly administered CYP2C19 inducers and inhibitors on pantoprazole's pharmacokinetic (PK) behaviour.

Methods

Patients and study design

Patients were from two cohorts in our institution. Cohort I ($n = 8$) was a group of patients analysed retrospectively. When physicians started to prescribe i.v. pantoprazole in 2002, they requested that in the absence of dosing recommendations, pantoprazole concentrations be obtained for some patients. These concentrations were measured after 2–18 days of pantoprazole treatment. Results were available within 24 h, allowing modifications to dose or dosing interval, if judged necessary by the attending physician, based on data from adults. All concomitant medications known to be inducers or inhibitors of CYP2C19 were recorded, as were hepatic parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin and International Normalized Ratio (INR)], if available.

Cohort II ($n = 12$) was from a single-centre, open-label Phase I/II study evaluating the pharmacokinetics and pharmacodynamics of i.v. pantoprazole in paediatric intensive care patients. This trial started in February 2004 and is still ongoing due to interesting unexpected pharmacodynamic data [33]. Patients between the ages of 0 and 18 years at time of entry into the paediatric intensive care unit were potential candidates for enrolment. Patients were eligible for study inclusion if they presented at least one risk factor (respiratory failure, coagulopathy or Pediatric Risk of Mortality score $\geq$10) for the development of clinically significant stress-related upper gastrointestinal bleeding [34] or if they had been prescribed stress ulcer prophylaxis by their attending physician. Other inclusion criteria included an anticipated length of stay in the intensive care unit of $\geq$24 h, presence of an arterial, central venous or peripheral line for blood drawing, informed consent from a parent or legal guardian and approval of the attending physician. Patients were excluded if there was known hypersensitivity to PPIs, INR >1.5 secondary to hepatic disease or if they were receiving concomitant administration of known inducer(s) or inhibitor(s) of CYP2C19. The initial dosage regimen of pantoprazole was 20 mg/1.73 m^2/day in neonates and 40 mg/1.73 m^2/day for patients >1 month old, administered once a day. This dosage regimen was extrapolated from the recommended adult dose (40 mg once a day) scaled to body surface area (BSA) [35]. PK evaluation was performed during the first dose of pantoprazole in all of these patients. A protocol for increasing pantoprazole dose was planned if there was inadequate gastric acid suppression, with the highest dose being 80 mg/1.73 m^2/day. Adverse events most frequently reported for pantoprazole were monitored daily [36]. The study protocol and consent forms were approved by the Research Ethics Committee of Centre Hospitalier Universitaire Sainte-Justine.

Measurement of pantoprazole concentrations

Pantoprazole was administered as an infusion over 15–30 min. Serial blood samples (0.5 ml) were collected in heparinized tubes just prior to and at 0, 0.25, 0.75, 1, 2, 4, 6 and 12 h (cohort I) or just prior to and at 0, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h (cohort II) after the end of pantoprazole infusion. Plasma was immediately separated and stored at −70 °C until assayed. Pantoprazole concentrations were determined using a high-performance liquid chromatography (HPLC) method with a diode array detector set at 290 nm (series 1100; Agilent Technologies, Santa Clara, CA, USA). To a volume of 50 µl of plasma, 25 µl of internal standard (phenacetin) working solution (at a concentration of 20 µg ml^{-1}) and 100 µl of acetonitrile were added. After mixing vigorously and centrifugation, a 130-µl aliquot of supernatant was transferred to a propylene vial, dried and reconstituted in a 100-µl mixture of acetonitrile and water (1:3). The mixture was pipetted into an autosampler vial and aliquots of 50 µl were injected into the HPLC system. Chromatographic separation occurred using a Nova-Pak C_{18} column with a mobile phase composed of acetonitrile and 10 mM ammonium acetate buffer, pH 6.5 (25:75) and mixing at a flow rate of 1.2 ml min^{-1}. Pantoprazole concentrations were quantified by height ratios. The lower and upper limits of quantification were 0.1 mg l^{-1} and 25 mg l^{-1}, respectively. The within-run and between-run coefficients of variation for the assays were <10%. For quality control, four concentrations were used (0.5, 2, 5 and 10 mg l^{-1}). The coefficients of variation for these controls were <5%.

Population pharmacokinetic analysis

The PK parameters were estimated using a population pharmacokinetic (POPPK) approach. The analysis was carried out with the software package NONMEM, version VI (Level 1.2, NONMEM Project Group, ICON Development Solutions, USA) using the first-order conditional estimation method with the interaction option [37].

Model development The initial step in the modelling process was the definition of a basic structural POPPK model without covariates. One- and two-compartment models with zero-order infusion and first-order elimination were tested. Model parameters were clearances and volumes of distribution: total clearance (CL) and central volume of distribution (V_c) for the one-compartment model and CL, intercompartmental clearance (Q), V_c and peripheral volume of distribution (V_2) for the two-compartment model. Model selection was based on: (i) visual inspection of the scatter plots of observed concentrations *vs.* population and individual predictions; (ii) visual inspection of the scatter plots of weighted residuals (WRES) *vs.* population predictions and time; and (iii) the objective function value (OFV), which is proportional to the −2 log likelihood. A decrease of 3.84 was considered statistically significant for the addition of one parameter (corresponding to a $P \leq 0.05$). To help visualize trends in the plots a LOESS fit, which is a form of locally weighted polynomial regression, was superimposed when appropriate. At each point in the dataset a polynomial is fit to a subset of the data, with explanatory variable values near the point whose response is being estimated. The weight of the fit is inversely proportional to the distance from the point whose response is being estimated [38].

Fixed effects parameters were used to describe the typical population estimates, and an exponential random effect model was used to describe interindividual variability for each model parameter:

$$\theta i = \theta \exp(\eta i)$$

where θi is the estimated parameter value for the i^{th} individual, θ is the fixed effect typical parameter value in the population, and ηi are individual-specific random effects for the i^{th} individual symmetrically distributed with zero mean and variance ω.

The potential covariance of the parameters was also investigated with full blocks of ωs. A combined proportional and additive error model was used to model the residual unexplained variability,

$$C_{ij} = \hat{C}_{ij} + \hat{C}_{ij} \cdot (\varepsilon_{ij1}) + \varepsilon_{ij2}$$

where C_{ij} is the j^{th} observed concentration at time point j for the i^{th} individual, $\hat{C}_{ij}$ is the j^{th} predicted concentration at time point j for the i^{th} individual and ε_{ij1} and ε_{ij2} are residual random errors for the j^{th} concentration of the i^{th} individual symmetrically distributed with zero means and variances σ_1 and σ_2.

The second step in the model construction was to build an allometrically scaled model that considers the effects of body size (body weight or BSA) in the base model. After allometrically scaling the model, the following covariates that could influence pantoprazole PK parameters were examined: age, sex, presence or absence of SIRS [39], hepatic dysfunction (total bilirubin ≥4 mg dl^{-1} or ALT two times the upper limit of normal for age) [39], and concomitant treatment with CYP2C19 inhibitors or inducers. Continuous covariates were tested using a power model as shown in the following equation:

$$\text{PK parameter} = \theta_{pop} \times (\text{covariate}/\text{covariate}_{median})^{\text{estimated power}}$$

where θ_{pop} is the population mean and $\text{covariate}_{median}$ is the median of the total population covariate. The power factor for body weight was fixed at 0.75 for clearances and 1 for volumes, as is common practice in paediatric studies [40]. Dichotomous covariates were tested using the following equation:

$$\text{PK parameter} = \theta_{pop} \times (\text{estimated effect for covariate})^{\text{dichotomous covariate}}$$

where a dichotomous covariate was coded as 1 if present, and 0 otherwise.

Visual inspection of scatter plots of WRES *vs.* covariates and differences between the individual and population parameter *vs.* covariates were used to guide selection and testing of different models. An automated generalized additive model algorithm was also used to aid covariate selection. A stepwise forward selection approach was used for covariate inclusion. Covariates were included in the model for $P \leq 0.05$. Backward elimination was then performed where each covariate was independently removed from the model to confirm its relevance. An increase in the OFV of ≥ 6.7 ($P \leq 0.01$) was necessary to confirm that the covariate was significant.

Model validation A predictive check method was used to evaluate the model performance [41]. The point parameter estimates, interindividual variability and residual variability obtained from the final model were used to generate 1000 simulated datasets. The distribution of the simulated AUCs was then compared with the originally observed AUCs. A predictive check *P*-value, defined as the probability that the simulated AUCs could be greater than the median observed AUC, was calculated.

A nonparametric bootstrap ($n = 1000$ samples) was used to evaluate the stability and precision of the final model parameters [42]. Only runs that converged successfully were used for further analysis. The final parameter estimates were compared with the median of the bootstrap results. The 95% confidence intervals were calculated as the 2.5th and 97.5th percentiles from the bootstrap distribution.

Model prediction Using the final POPPK model, we simulated the changes in CL expressed per kg of body weight during childhood growth. For all simulations, 50th percentile body weight for boys was used (http://www.cdc.gov/growthcharts). Pantoprazole AUCs were also predicted from the final model. CL estimates of children presenting none, one or multiple significant covariates and receiving a daily dose of 40 mg/1.73 m^2 were considered for the calculation of the AUC values. The following equation was used to compute $AUC_{0-24\,h}$: 40 mg × BSA/1.73 m^2/estimated CL.

Results

Patient population

Twenty patients (13 boys, 7 girls) from 10 days to 16.4 years of age were included in the study. Demographic data, underlying disease(s), indications and doses of pantoprazole, patient hepatic function, inflammatory status and concomitant medications are summarized in Table 1. The median daily dose of pantoprazole was 41.8 mg/1.73 m^2/day (19.9–140.6). Although the highest dose planned in the protocol was 80 mg/1.73 m^2/day (cohort II), one patient received 140.6 mg/1.73 m^2/day due to a prescription error, but there were no clinical consequences. Pantoprazole was given intravenously once a day to all patients except one patient, who received it twice daily. Seven patients met the criteria for SIRS. Three patients from cohort I received medications known to inhibit CYP2C19 (fluconazole, voriconazole, and isoniazid) and one received both a CYP2C19 inhibitor (fluconazole) and a CYP2C19 inducer (rifampicin). No patients were excluded. Pantoprazole was well tolerated by all patients.

Table 1

Summary of patient characteristics

Variable [median and (range) or *n*]	Cohort I (*n* = 8)	Cohort II (*n* = 12)	All patients (*n* = 20)
Age (years)	9.4 (2.4–16.4)	0.7 (0.03–4.0)	2.1 (0.03–16.4)
Weight (kg)	30.6 (16.0–84.5)	6.8 (2.7–17.9)	12.7 (2.7–84.5)
Body surface area (m^2)	1.06 (0.66–1.96)	0.36 (0.20–0.71)	0.57 (0.20–1.96)
Underlying disease(s)			
Open heart surgery	0	10	10
Hepatic diseases or transplantation	4	0	4
Haematological disorders	2	0	2
Respiratory failure	1	1	2
Shock	0	1	1
Polytrauma	1	0	1
Indication for i.v. pantoprazole			
Stress ulcer prophylaxis	0	12	12
Refractory epigastric pain*	5	0	5
Upper gastrointestinal bleeding	3	0	3
Pantoprazole dose†			
mg/1.73 m^2/day	49.1 (35.3–76.3)	39.8 (19.9–140.6)	41.8 (19.9–140.6)
mg/kg/day	1.0 (0.5–1.9)	1.3 (0.9–4.6)	1.1 (0.5–4.6)
Hepatic dysfunction	4	1‡	5
SIRS	4	3	7
Concomitant medications			
CYP2C19 inhibitor	4	0	4
CYP2C19 inducer	1	0	1

*Despite treatment with omeprazole or ranitidine. †Pantoprazole was given once a day with the exception of one patient in cohort I, who received it twice daily. ‡Alanine aminotransferase twice the upper limit of normal for age but International Normalized Ratio <1.5. i.v., intravenous; SIRS, systemic inflammatory response syndrome.

Population pharmacokinetic analysis

The POPPK analysis included 156 plasma concentration measurements. A two-compartment model with zero-order infusion and first-order elimination best fit the data. Initially the effect of body size alone was investigated as a potential predictor for PK parameters. After investigation of different measures of body size (body weight or BSA), body weight proved to be the most significant size measurement to explain variability in PK parameters. As such, all PK parameters (CL, V_c, Q, V_2) were allometrically scaled to

Table 2

Summary of covariate effects on pantoprazole clearance (only significant effects are reported)

Covariate*	OFV decrease
SIRS	17.8
Age	7.5
CYP2C19 inhibitor	6.9
Hepatic dysfunction	9.4

*Introduced in the model in the listed order. OFV, objective function value; SIRS, systemic inflammatory response syndrome.

body weight. After incorporation of the allometric relationships, the OFV decreased by 63.7. Among other covariates tested for CL, SIRS, age, CYP2C19 inhibitors and hepatic dysfunction produced a significant decrease in OFV (Table 2). Only body weight significantly influenced V_c, Q and V_2.

The final POPPK model was described by the following equations:

$$\mathrm{CL}\ (\mathrm{l\,h^{-1}}) = 5.28 \times (\mathrm{WT}/20)^{0.75} \times 0.377^{\mathrm{SIRS}} \times (\mathrm{AGE}/5)^{0.316} \times 0.342^{\mathrm{INH}} \times 0.495^{\mathrm{HEP}}$$

$$V_c\ (\mathrm{l}) = 2.22 \times (\mathrm{WT}/20)$$

$$Q\ (\mathrm{l\,h^{-1}}) = 1.10 \times (\mathrm{WT}/20)^{0.75}$$

$$V_2\ (\mathrm{l}) = 2.73 \times (\mathrm{WT}/20)$$

where body weight (WT) is in kg, age in years and dichotomous covariates [SIRS, CYP2C19 inhibitors (INH) and hepatic dysfunction (HEP)] coded as 1 if present and 0 otherwise. Parameter estimates for the final model are summarized in Table 3.

Based on individual parameter estimates, the median (range) values for CL, volume of distribution at steady state and elimination half-life ($t_{1/2}$) for patients aged between 1 month and 5 years included in this study were 0.14 l h^{-1} kg^{-1} (0.01–0.26), 0.22 l kg^{-1} (0.09–0.52) and 2.0 h (0.7–11.8), respectively.

The total interindividual variability for CL in the base model was estimated to be 132.7% (100%). The variability of each significant covariate identified, body weight, SIRS, age, CYP2C19 inhibitors and hepatic dysfunction, was 39.4% (29.7%), 33.4% (25.1%), 11.3% (8.5%), 1.7% (1.3%) and 14.3% (10.8%), respectively. The unexplained variability for CL was 32.5% (24.5%). Pantoprazole CL increased with weight and age, whereas the presence of SIRS, CYP2C19 inhibitors and hepatic dysfunction, when present separately, significantly decreased pantoprazole CL by 62.3, 65.8 and 50.5%, respectively. The total interindividual variability for V_c in the base model was estimated to be 137.5% (100%). Body weight was the only significant covariate identified and represented 96.9% (70.5%) of this total variability, with an unexplained variability of 40.6% (29.5%).

Goodness of fit plots obtained for the final POPPK model are shown in Figure 1. The POPPK model evaluation, which included the results of a predictive check and non-parametric bootstrap analysis, revealed that the final model provided a reliable description of the data. The predictive performances of the final POPPK model for AUC are shown in Figure 2. Pantoprazole plasma concentrations were within the 90% prediction intervals. The simulated AUC distribution was centred on the median of the original data with a predictive check P-value of 0.52. The final model was then subjected to a bootstrap analysis. As shown in Table 3, the median values were similar to the parameter estimates of the original dataset, and all parameters obtained from the original dataset were included in the 95% confidence interval calculated from the 927 successful runs (out of 1000).

The final POPPK model was used to simulate pantoprazole CL and AUCs of children between 1 month and 5 years of age. The magnitude of the covariate effects on CL is depicted in Figure 3A, and simulated AUCs for a daily dose of pantoprazole of 40 mg/1.73 m^2 are shown in Figure 3B. As illustrated, children between the ages of 6 months and 5 years without SIRS and hepatic dysfunction and not taking any CYP2C19 inhibitor exhibited AUC values from 3.5 to 7.0 mg h^{-1} l^{-1}. In contrast, children presenting either SIRS, hepatic dysfunction or taking CYP2C19 inhibitors attained higher AUCs with the same daily dose, with the highest AUC values occurring in children exhibiting all three covariates simultaneously.

Discussion

To our knowledge, this study is the first systematic investigation of the pharmacokinetics of i.v. pantoprazole in the paediatric population as well as in paediatric intensive care patients. The POPPK analysis revealed important interindividual variation for each kinetic parameter. Body weight and SIRS were the two most important covariates for CL, accounting for 54.8% of total variability. Body weight was the only significant covariate identified for V_c. The final population model had an unexplained interindividual variability of 32.5 and 40.6% for CL and V_c estimates, respectively.

As the first step of POPPK model building, we developed an allometrically scaled model that considered the effects of body size, since CL usually increases with growth and occasionally V_c. Among the allometric covariates tested, body weight was the first one to be introduced in our model, as recommended [43]. Body weight, and to a lesser degree age, were associated with pantoprazole CL, with a nonlinear increase in CL with increasing weight and age (Figure 3A). These changes in CL with growth are

Table 3

Parameter estimates for the final model with bootstrap validation

Parameter	Parameter estimates (RSE%)†	Bootstrap* Median	Bootstrap* 95% CI
Pharmacokinetic parameters‡			
CL (l h^{-1})	5.28 (10.9)	5.08	3.88, 6.90
V_c (l)	2.22 (12.3)	2.20	1.54, 2.83
Q (l h^{-1})	1.1 (19.0)	1.1	0.7, 1.6
V_2 (l)	2.73 (25.3)	2.69	1.76, 6.04
Interindividual variability (IIV)§			
IIV CL (%)	32.5 (1.5)	27.0	10.5, 37.8
IIV V_c (%)	40.6 (3.0)	39.5	21.3, 68.6
IIV Q (%)	24.7 (1.4)	27.3	7.7, 62.1
IIV V_2 (%)	98.1 (20.4)	93.9	52.6, 169.9
Residual variability			
Residual additive error (SD in mg l^{-1})¶	0.00001		
Residual proportional error (%)§	19.5 (22.5)	19.0	13.1, 23.6
Covariates††			
SIRS covariate effect	0.377 (28.5)	0.405	0.160, 0.784
Age covariate effect	0.316 (12.4)	0.320	0.206, 0.407
CYP2C19 inhibitor covariate effect	0.342 (37.1)	0.342	0.125, 0.800
Hepatic dysfunction covariate effect	0.495 (20.9)	0.501	0.291, 0.904

*Median of 927 successful bootstrap samples from the 1000 runs with prediction intervals calculated as the 2.5th and 97.5th percentiles. †Relative standard error calculated as the standard error of parameter estimate/parameter estimate × 100%. ‡CL, typical value of total clearance; V_c, typical value of the central volume of distribution; Q, typical value of the intercompartmental clearance; V_2, typical value of the peripheral volume of distribution. The typical values refer to a patient with a body weight of 20 kg, age of 5 years, without SIRS, CYPC19 inhibitor and hepatic dysfunction, according to the final model. §Interindividual variability (IIV) and residual proportional error are given as an approximate CV (square root of the variance). ¶The additive error was fixed in the model. ††Body weight was included in all pharmacokinetic parameters as an allometric fixed term. All other covariates included in the table had an effect on CL. SD, standard deviation; SIRS, systemic inflammatory response syndrome.

somewhat in agreement with the findings of Koukouritaki *et al.* [44] who investigated the developmental expression of human hepatic CYP2C19, the enzyme responsible for most pantoprazole metabolism. The authors found that CYP2C19 protein and catalytic activities were 12–15% of mature values throughout gestation, increased linearly over the first five postnatal months and nonlinearly thereafter, with important interindividual variability. However, comparison with this *in vitro* study is limited by the fact that other age-related factors that could influence pantoprazole CL, such as relative liver size (expressed as a percentage of total body weight) and changes in protein binding, are not accounted for.

SIRS, a nonspecific inflammatory process occurring after a variety of insults such as trauma, infection, burns, pancreatitis and other diseases, was also identified as a significant covariate. Its presence was associated with a 62.3% decrease in pantoprazole CL. One may speculate that SIRS decreases the activity of the enzymes responsible for pantoprazole elimination, i.e. CYP2C19 and CYP3A4. This hypothesis is supported by data demonstrating that inflammation, both *in vitro* and *in vivo*, affects drug metabolism by downregulating several hepatic enzymes [45, 46]. Two studies focusing on the activity of cytochrome P450 in critically ill patients have reached similar conclusions. Carcillo *et al.* found a two- to 10-fold reduction in mixed cytochrome P450 activity, as measured by antipyrine clearance, in children with multiple organ failure, a more advanced stage of SIRS [47]. In adults, acute inflammation after elective surgery was associated with a significant decline in CYP3A4 activity measured by the erythromycin breath test [48]. Beyond the impact of SIRS on pantoprazole elimination, our findings suggest that SIRS may be a new clinical parameter to be considered for dosing adjustment in paediatric intensive care patients for drugs with a narrow therapeutic index or those not titrated to response. This has important clinical consequences considering that up to 80% of paediatric intensive care patients present a SIRS [49] and that many drugs administered in the intensive care setting are metabolized by the cytochrome P450 enzyme system (pantoprazole being one of these drugs).

In the final POPPK model constructed in this study, CL decreased with hepatic dysfunction. This is not surprising considering that pantoprazole is primarily metabolized by the liver. Data from adults had previously shown alterations in pantoprazole pharmacokinetics among patients with moderate to severe hepatic impairment [50]. Drug interactions were also investigated as a potential covariate. Although no clinically significant drug interactions have been reported between pantoprazole and a range of agents in healthy adult volunteers [51], concomitant administration of CYP2C19 inhibitors was identified as a significant covariate affecting CL in our paediatric intensive care patients.

Using our final POPPK model, predicted pantoprazole CLs and AUCs were determined for children aged between

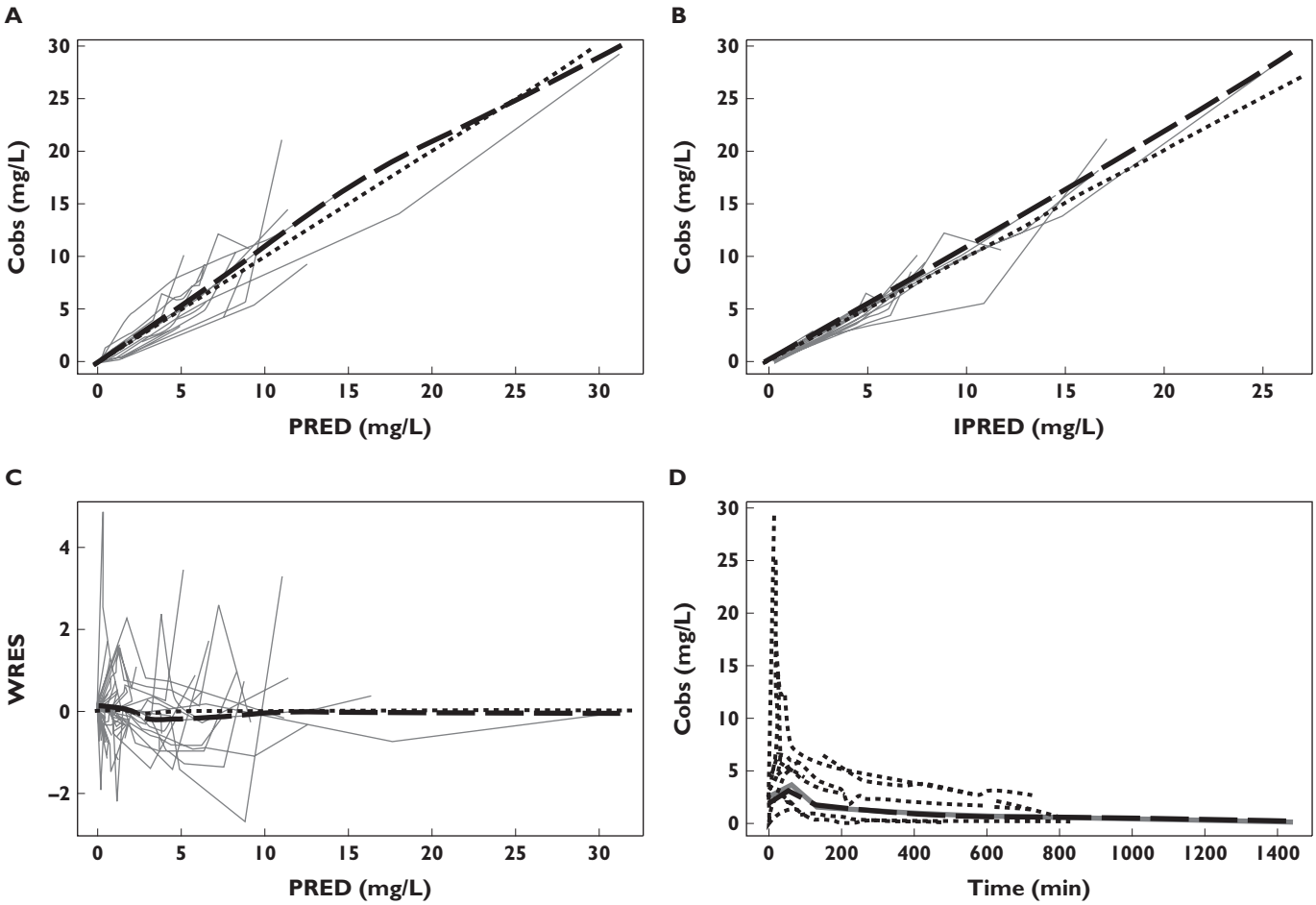

Figure 1

Goodness of fit plots of the final model for pantoprazole. The heavy broken lines are smoothings (LOESS) of the ordinate values. Dotted lines are identity lines in panels A and B and a zero line in panel C. (A) Observed concentrations (Cobs) *vs.* population model predicted concentrations (PRED). (B) Cobs *vs.* individual model predicted concentrations (IPRED). (C) Weighted residual (WRES) *vs.* PRED. (D) Cobs *vs.* time with LOESS of Cobs *vs.* time and LOESS of PRED *vs.* time. A, INDIVIDUAL (—); IDENTITY (▪▪▪▪); LOESS (▬ ▪); B, INDIVIDUAL (—); IDENTITY (▪▪▪▪); LOESS (▬ ▪); C, INDIVIDUAL (—); ZERO (▪▪▪▪); LOESS (▬ ▪); D, INDIVIDUAL (▪▪▪▪); LOESS PRED (▬); LOESS Cobs (▬ ▪)

1 month and 5 years presenting one, multiple, or no significant covariates and receiving the recommended adult daily dose expressed in terms of BSA (40 mg/1.73 m^2/day) (Figure 3). Simulations were not made for neonates and children >5 years old considering the small number of patients enrolled in these age groups (two neonates and four children >5 years old with none between 6 and 13 years). For paediatric intensive care patients aged between 1 month and 5 years without SIRS, hepatic dysfunction and not taking CYP2C19 inhibitors, the predicted pantoprazole CL is either similar (<6 months) or faster (>6 months) than that reported in healthy adult subjects (0.06–0.14 l h^{-1} kg^{-1}) [52, 53]. This finding, i.e. faster drug clearance in children compared with adults, has been shown for many drugs, although the exact underlying mechanism remains unclear [54]. Relative increase in liver size in children compared with adults may contribute to such a finding [55]. Even though the predicted pantoprazole CL is faster in patients >6 months old, the predicted pantoprazole AUC values in these patients (Figure 3B) are within the range of AUC values (mean 5.2 mg h^{-1} l^{-1}; 68% range 3.86–7.00 mg h^{-1} l^{-1}) reported from a previous adult study in which healthy volunteers received a single i.v. dose of pantoprazole (40 mg) [53]. The reason for this is most likely to be secondary to the fact that our simulations were made with BSA-based dose, which usually yields higher adult-referenced bodyweight base dosage, especially in young infants [35]. In contrast, for paediatric patients from 1 month to 5 years of age presenting either SIRS, hepatic dysfunction and/or taking CYP2C19 inhibitors, the predicted pantoprazole CL is slower than that reported in adults with much higher predicted AUC values.

To date, two paediatric trials have studied the pharmacokinetics of pantoprazole [22, 23]. One included 14 paediatric intensive care patients between 2 and 16 years of age receiving i.v. pantoprazole [22]. The only kinetic

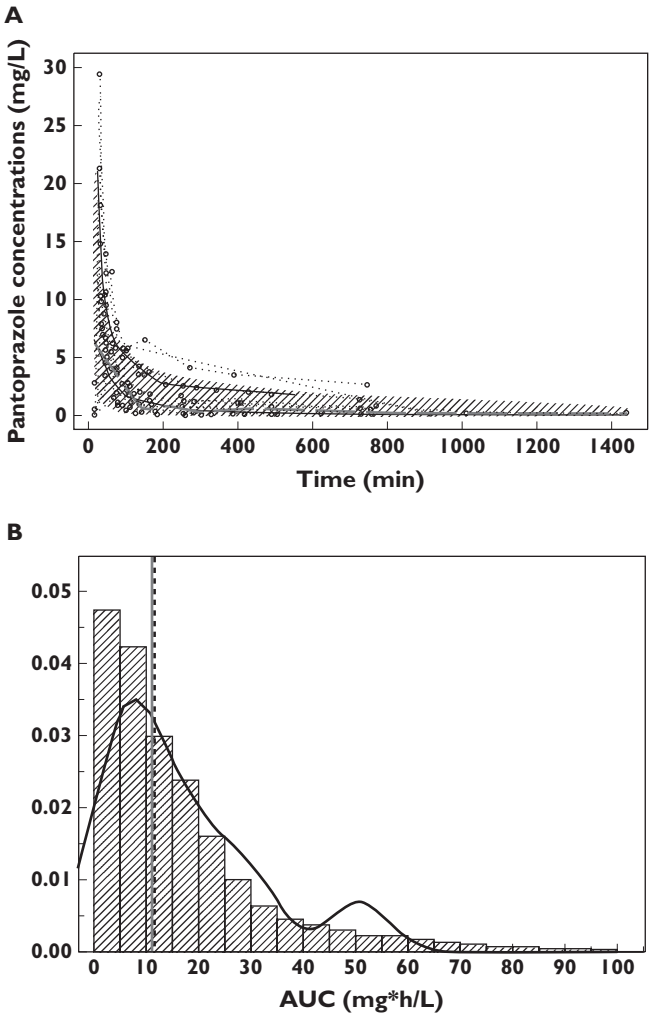

Figure 2

Predictive check results. (A) Pantoprazole plasma concentrations with the 90% prediction intervals (PI) from the final population model. Observed plasma concentrations (Cobs) for each patient are shown as circles joined by a dotted line. The hatched area represents the 90% PIs and the solid black line the median. The dashed line represents a smoothing of the population prediction (PRED) from the final model (LOESS). (B) The histogram represents the simulated area under the plasma concentration–time curve during the sampling time (AUC_{0-t}) from the final model. The distribution of the observed AUC_{0-t} is shown as a black line. The median of the observed AUC_{0-t} and the individual predicted AUC_{0-t} are shown as a bold grey line and a black dashed line, respectively. The model adequately simulates the AUC_{0-t} evidenced by a *P*-value of 0.52. A, Cobs (∘·∘·∘); LOESS PRED (— ⁻); MEDIAN, 90% PI (—⁄⁄⁄); B, Simulated AUC (▨); Median simulated AUC (▪▪▪); Distribution of the observed AUC (—); Median observed AUC (——)

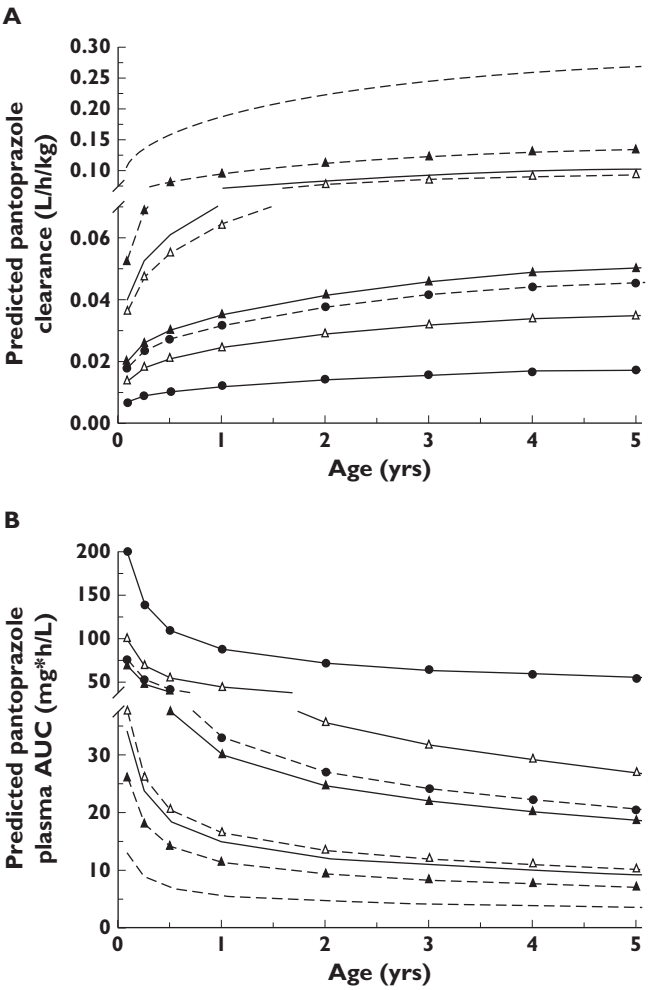

Figure 3

The magnitude of covariate effects on pantoprazole CL and AUC. Predicted CL values were calculated using the final population model and 50th percentile body weight for children between 1 month and 5 years old, whereas AUCs were determined for an adult pantoprazole dose of 40 mg/1.73 m^2. (A) Predicted CLs and (B) AUCs in the absence (dashed lines) or presence (solid lines) of systemic inflammatory response syndrome (SIRS) and without the influence of any other covariates are presented as a function of age. The influence of other covariates on pantoprazole CL and AUC in non-SIRS and SIRS conditions is also illustrated: inhibitor(s) of CYP2C19 (open triangle), hepatic dysfunction (closed triangle) and a combination of inhibitor(s) of CYP2C19 and hepatic dysfunction (closed circle)

parameter reported in the study was the mean $t_{1/2}$, which was shorter than the median $t_{1/2}$ observed in our patients (1.1 ± 0.5 h compared with 2.0 h (0.7–11.8 h)). The available data prevent any comparison between those critically ill paediatric patients and those included in our study in terms of severity of illness, hepatic impairment, CYP2C19 genetic status or drug interactions.

The second study was performed in 24 noncritically ill paediatric patients, between 6 and 16 years old, who received pantoprazole orally and included 21 extensive and three poor CYP2C19 metabolizers [23]. Among the extensive metabolizers, the mean apparent CL (CL/*F*) was 0.30 l h^{-1} kg^{-1}. One needs to be cautious when comparing these results with our data, since the route of administration was different and the bioavailability of pantoprazole after oral administration is unknown in children. However, using the adult value for pantoprazole bioavailability (*F* = 77%) [56], the mean systemic CL of the extensive

metabolizers studied by Kearns *et al.* [23] would approximate 0.23 l h^{-1} kg^{-1}. This is similar to the pantoprazole CL predicted from our final POPPK model for patients aged 2–5 years without SIRS, hepatic dysfunction and not taking CYP2C19 inhibitors (Figure 3A). In contrast, for patients presenting one or many of these factors, predicted pantoprazole CL are lower than that reported by Kearns *et al.* [23]. A similar decrease in omeprazole CL attributed to slower metabolism had been previously found in critically ill paediatric transplant patients [31]. Omeprazole $t_{1/2}$ in those subjects was much longer compared with $t_{1/2}$ in children with refractory acid-related disorders and adults.

Even though the efficacy of PPIs has been shown to correlate with the AUC both in adults [16, 24–26] and in children [27, 28], the lack of a known paediatric target AUC for pantoprazole prevents the use of our model to derive specific dosing recommendations. In fact, there is some evidence suggesting that the pharmacokinetic–pharmacodynamic relationship is different for critically ill children compared with that of adults, with much higher pantoprazole AUC values needed to raise intragastric pH in paediatric intensive care patients [33]. Furthermore, there may be more than one paediatric target AUC depending on the clinical condition for which pantoprazole is given. For example, a higher AUC may be required for the treatment of upper gastrointestinal bleeding compared with the prevention of stress-related ulcer bleeding considering that gastric pH > 6 is required for the former indication [57, 58], whereas a gastric pH > 4 is recommended for the latter [59].

Another question raised by our results is whether or not there is a pantoprazole AUC value above which side-effects may occur. In other words, is there cause for concern for a 3-year-old patient with SIRS, hepatic dysfunction and taking CYP2C19 inhibitors who, according to our final PK model, has a predicted pantoprazole AUC value about 20 times higher that that reported in adults receiving the same dose (40 mg/1.73 m^2/day)? Unfortunately, our study was not designed to determine the safety of pantoprazole in paediatric intensive care patients, and this question remains unanswered. In adults, there are concerns and controversy surrounding the potential complications of sustained high PPI plasma levels and overt gastric acid suppression. Conditions that increase the gastric pH, namely treatment with histamine$_2$ receptor antagonists or PPIs, have been associated with colonization of normally sterile upper gastrointestinal tract and bacterial proliferation in the stomach [60, 61]. The sequence of events can then lead to either alteration of the normal colonic microflora, a risk factor for *Clostridium difficile*-associated diarrhoea, or retrograde transmission of gastric microorganisms into the trachea, a possible pathogenic route for ventilator-associated pneumonia [61, 62].

This study has some limitations. One may argue that an important covariate was not tested in the present study, namely patient CYP2C19 genetic status. CYP2C19 displays a known genetic polymorphism characterized by two phenotypes of varying metabolic capacity, which could have accounted for some of the variation observed in our PK parameters [63]. Indeed, poor metabolizers experience higher PPI AUCs compared with both heterozygous and homozygous extensive metabolizers, for whom there is a substantial overlap [64]. Another limitation of the final model is the small number of patients ($n = 20$), which may inflate the type I error when a forward stepwise covariate addition is used [65]. This small sample size means that there are limited patients across various age groups, i.e. neonates, infants, children and adolescents, with very few patients >5 years old and no patient in the 6–13 years age group. This sparseness of data below 1 month and beyond 5 years old limits the use of the model to predict pantoprazole dosing regimen in these age groups. Therefore, CL and AUC simulations were restricted for children from 1 month to 5 years of age. In addition, the accuracy of simulation using parameter estimates and their variability could be impaired if applied to children with milder diseases, since the subjects involved in the model-building process were paediatric intensive care patients.

In conclusion, the pharmacokinetics of i.v. pantoprazole in paediatric intensive care patients is extremely variable. As shown by our POPPK model, developmental changes inherent to the paediatric population, as well as factors frequently encountered in the paediatric intensive care unit such as SIRS, hepatic dysfunction and concomitant drug administration, were able to explain most of this variability. Our results provide important information to healthcare providers regarding how to select a starting dose and dosing regimen for pantoprazole in paediatric intensive care patients, especially for infants and children aged between 1 month and 5 years. Further studies are needed to define better the efficacious and safe pantoprazole AUCs for the prevention of bleeding from stress-induced ulcers and the management of upper gastrointestinal bleeding in this population.

Competing interests

None declared.

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